Citation:

White AM, Johnston CS, Swan PD, Tjonn SL, Sears B. Blood ketones are directly related to fatigue and perceived effort during exercise in overweight adults adhering to low-carbohydrate diets for weight loss: A pilot study. *J Am Diet Assoc*. 2007 Oct; 107 (10): 1,792-1,796.

PubMed ID: 17904939

Study Design:

Randomized Controlled Trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To explore how low-carbohydrate diets impact weight loss, desire to exercise, fatigue, and perceived effort during exercise in untrained, overweight adults adhering to ketogenic or to non-ketogenic low-carbohydrate, hypocaloric diets for two weeks.

Inclusion Criteria:

- Ages 20 to 60 years
- Overweight [body mass index (BMI) >25kg/m^2]
- Free from diagnosed disease
- Non-smokers
- Not regularly taking prescription medications
- Not pregnant.

Exclusion Criteria:

Not described.

Description of Study Protocol:

Recruitment

Subjects were recruited from a campus population using electronic message boards and posted flyers.

Design

- This study used a prospective RCT design and participants were stratified by age, sex, and BMI, and were assigned to either a ketogenic or non-ketogenic diet group
- Participants were instructed to continue their typical activity patterns and to not initiate an exercise program during the two-week trial.

Dietary Intake/Dietary Assessment Methodology

Not applicable.

Blinding Used

- Participants were aware of diet differences between groups because the lunch meal was consumed in a common setting
- Study personnel collecting exercise data and scoring the Profile Mood States questionnaire were unaware of the diet assignments.

Intervention

- Participants were provided with all foods consumed during the two-week study period. A 14-day menu was developed by a registered dietitian (RD)
- Participants were served a hot lunch daily Monday through Friday; all other meals and snacks were packaged and consumed at home
- Energy intake was strictly controlled to provide approximately 70% of that needed for weight maintenance
- The diets were:
    - Ketogenic: 5% carbohydrate, 65% fat, 30% protein
    - Non-ketogenic: 40% carbohydrate, 30% fat, 30% protein.

Statistical Analysis

- Repeated measures analysis of variance, with main effects of time and time X group interactions, was used to assess differences in metabolic data
- Spearman correlation test was used to evaluate relationships between variables
- Significance was set at $P \leq 0.05$.

Data Collection Summary:

Timing of Measurements

- Exercise testing, body weight, and fat mass were assessed at baseline and at two weeks
- 24-hour urine samples were collected the day before exercise and immediately after exercise.

Dependent Variables

- Body weight: Measurement technique not reported
- Fat mass: Measured using the Tanita Body Composition Analyzer
- Urinary urea nitrogen: Measured using 24-hour urine sampling
- Sub-maximal exercise testing was done by having subjects perform a 90-minute walk at 50% to 79% of their predicted heart rate
- Oxygen consumption (VO_2) and respiratory exchange ratio (RER) were measured using indirect calorimetry using a metabolic cart. VO_2 and RER were measured from three-minute gas samples collected at 10-minute intervals during the exercise test. Substrate utilization

was calculated using the proteinrespiratory quotient (RQ) derives from the urinary nitrogen and metabolic (VO_2 and VCO_2) measures
- Rating of perceived exertion (RPE): Measured using a 20-point Borg scale at 10-minute intervals during the exercise testing
- Profile of Mood States scale: Assessed immediately after the exercise test was complete; assess six distinct mood states (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment).

Independent Variables

Macronutrient proportion of the diet:

- Ketogenic: 5% carbohydrate, 65% fat, 30% protein
- Non-ketogenic: 40% carbohydrate, 30% fat, 30% protein.

Description of Actual Data Sample:

- *Initial N:* N=20; 4 men and 16 women
  - Ketogenic diet: Two men, eight women
  - Non-ketogenic diet: Two men, eight women
- *Attrition (final N):* N=19, four men and 15 women
  - Ketogenic diet: Two men, seven women (One woman was dropped during the first week due to arrhythmia)
  - Non-ketogenic diet: two men, eight women
- *Age:*
  - Ketogenic diet: 38.4±3.9 years
  - Non-ketogenic diet: 37.2±3.9 years
  - Age did not differ between diet groups
- *Ethnicity:* Not reported
- *Other relevant demographics:* None reported
- *Anthropometric and Physiologic Measures:* Baseline subject characteristics did not vary between diet groups
- *Location:* United States.

Summary of Results:

Anthropometric and Physiologic Characteristics of the Diet Groups at baseline and at two-weeks

	Baseline		Two-Weeks		P-value	
	Ketogenic	Non-ketogenic	Ketogenic	Non-ketogenic	Time	Time x Group
BMI (kg/m^2)	34.6±1.6	34.3±1.5	33.5±1.6	33.2±1.4	0.000	0.931
Weight (kg)	96.9±5.6	100.3±6.1	92.9±5.6	96.3±5.8	0.000	0.995
Fat mass (kg)	39.2±3.1	42.3±3.9	36.6±3.0	39.1±4.0	0.000	0.487

Blood β-hydroxybutrate (mmol/L)	0.09±0.02	0.10±0.02	0.72±0.18	0.20±0.03	0.001	0.010
Perceived rate of exertion	11.6±0.6	11.4±0.6	11.0±0.6	10.3±0.8	0.068	0.570
Respiratory exchange ratio	0.81±0.04	0.79±0.02	0.73±0.01	0.75±0.01	0.005	0.276
Energy expenditure (kcal/kg)	5.12±0.51	5.02±0.64	4.75±0.70	4.94±0.49	0.631	0.739
Fat expenditure (kcal/kg)	3.67±0.58	3.00±0.45	4.14±0.78	3.98±0.31	0.073	0.491
Carbohydrate expenditure (kcal/kg)	1.25±0.39	1.77±0.38	0.32±0.16	0.82±0.25	0.003	0.971
Protein expenditure (kcal/kg)	0.18±0.07	0.23±0.07	0.30±0.04	0.14±0.04	0.869	0.047
Urea nitrogen (mmol)	11.4±4.2	16.6±5.9	17.3±1.9	9.0±2.7	0.800	0.067
Average heart rate (bpm)	106.1±3.3	113.3±4.0	107.3±10.6	110.8±2.1	0.696	0.263
Exercise intensity (percentage heart rate max)	58.6±1.9	61.3±2.2	59.3±1.9	59.9±1.6	0.707	0.220

- Both diets were equally effective at inducing weight loss (~4kg after two weeks) (see Table)
- Blood β-hydroxybutrate (mmol/L) increased significantly in the ketogenic diet group compared to the non-ketogenic diet group after two-weeks (see Table)
- Respiratory exchange ratio (RER) decreased significantly in both diet groups between baseline and two-weeks (see Table)
- Exercise intensity did not change significantly over the two-week diet intervention for either diet group (see Table).

Other Findings

After two weeks of diet adherence, the participants perceived rate of exertion was directly related to blood ketones (r^2=0.221, P=0.049).

Author Conclusion:

- In this study, hypocaloric ketogenic and non-ketogenic diets induced significant weight loss over a two-week period; weight loss did not differ between the diet groups
- The ability and desire to maintain sustained exercise might be adversely impacted in individuals adhering to ketogenic diets for weight loss.

Reviewer Comments:

- *The small sample size used in this study limits generalizability*
- *This study was only two-weeks in length, so the longer term effects of consuming these diets is unknown.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	N/A
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	N/A
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes

3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A

6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	No
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes

8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	No
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes